Incident heart failure in patients with rheumatoid arthritis

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ORIGINAL RESEARCH

Incident Heart Failure in Patients With Rheumatoid Arthritis: A Nationwide Cohort Study

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***Background*—**Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with a wide range of comorbidities, including cardiovascular disease, but its association with heart failure (HF) is not fully clear. We investigated the risk of incident HF in a nationwide cohort of patients with RA.

***Methods and Results*—**The study comprised the entire Danish population aged ≥18 years followed from January 1, 2008 until first hospitalization for HF, emigration, December 31, 2012, or death. Information on comorbidity, medication, and socioeconomic status was identified by individual-level linkage of administrative registers. Patients with a rheumatologist diagnosis of RA between 1978 and 2008 were included. The primary study outcome was incident HF defined as first hospital admission for HF. Incidence rates of HF per 1000 person-years were calculated and incidence rate ratios adjusted for age, sex, calendar year, comorbidity, medications, socioeconomic status, smoking, and alcohol consumption were estimated. A total of 4 305 225 subjects with no history of HF were eligible for analysis at the study start. Of these subjects, 24 343 developed RA and 50 623 were hospitalized for HF. Overall incidence rates of incident HF were 2.43 and 6.64 for the reference population (n=49 879) and patients with RA (n=744), respectively. Correspondingly, the fully adjusted incidence rate ratio for incident HF was increased in patients with RA with incidence rate ratio 1.30 (95% confidence interval, 1.17–1.45).

***Conclusions*—**In this cohort study, RA was associated with an increased hospitalization for HF. These findings add significantly to the existing evidence of RA as a clinically relevant risk factor for HF. **(*J Am Heart Assoc*. 2018;7:e007227. DOI: 10.1161/JAHA.117.007227.)**

Key Words: cardiovascular disease • heart failure • inflammation • rheumatoid arthritis

Patients with rheumatoid arthritis (RA) and other chronic inflammatory disorders (eg, psoriasis and inflammatory bowel disease) suffer considerably increased cardiovascular morbidity and mortality when compared with the background population.[1–5] In patients with RA, the excess cardiovascular disease risk appears to be comparable with that found in patients with type 2 diabetes mellitus.[6,7] Both conventional cardiovascular risk factors (eg, hypertension, obesity, dyslipidemia, and diabetes mellitus) and increased systemic inflammation play a contributory role.[4,8,9]

Heart failure (HF) is a growing major public health problem that is also associated with increased inflammation and a high prevalence of cardiovascular risk factors.[10–12] The proinflammatory cytokines involved in HF promote myocardial damage

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/7/2/e007227/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this nationwide study, rheumatoid arthritis was associated with a 30% increased hospitalization for heart failure compared with the background population.

What Are the Clinical Implications?

- The findings add to the existing evidence that rheumatoid arthritis may be a clinically relevant risk factor for heart failure.
- Studies examining the value of more-extensive screening of these patients for heart failure are warranted.

and other pathogenic manifestations through an array of mechanisms, including, for example, increased arterial stiffness and endothelial dysfunction.[13–19]

Few studies have examined the risk of developing HF in patients with RA independent of cardiovascular risk factors.[13,17,20,21] The present study therefore aimed to investigate the risk of incident HF in a nationwide cohort of patients with RA by using Danish national administrative and healthcare registers.

Methods

Setting and Data Sources

Denmark maintains nationwide administrative and healthcare registers that offer a unique possibility for conducting large-scale epidemiological studies of several end points with a minimum loss to follow-up.[22–25] The Danish Civil Registration System established in 1968 allocates a permanent and unique civil registration number to each citizen at birth that allows unambiguous cross-linkage of data across nationwide registers.[24] In the present study, information on all pharmacy-dispensed prescriptions classified according to the Anatomical Therapeutical Chemical classification system was obtained from the Danish Registry for Medical Products Statistics.[22,26] This register was established in 1994 and records information on dispensing date, strength of the drug, and the allocated quantity.[22] Information on morbidity was retrieved from the Danish National Patient Register, which contains data on all inpatient hospital visits and diagnoses since 1978, and outpatient data since 1995 recorded according to the International Classification of Diseases (*ICD*) code.[23] Hospital-based pharmacological treatment (eg, biological therapy) is also coded in the Danish National Patient Register as treatment procedure (Sundhedvæsenets Klassifikations System) codes.[23] This coding of biological drug treatment has been validated previously.[27] Information on age, sex, vital status, and tax-reported household income was obtained from the Central Population Register and Statistics Denmark.[28] The guidelines for cohort studies as defined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were applied to the present study.[29]

Data availability

The data, analytical methods, and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Subjects

The study cohort comprised all Danes aged ≥18 years alive and resident in the source population on January 1, 2008 (the study start date). These individuals were then followed until the occurrence of the study end point, migration, death, or December 31, 2012, whichever came first. Patients with a diagnosis of HF (n=56 644) at baseline were excluded from the study cohort before the study start. Patients diagnosed with RA (*ICD* code M5–M6) between 1978 (when the Danish National Patient Register was established) and 2008 were identified (n=24 343). To ensure diagnostic accuracy, we only included diagnoses of RA made by rheumatologists. The primary outcome of interest was incident HF, defined as the first hospital admission for HF as primary or secondary discharge diagnoses (*ICD-10* Revision codes I42, I50, I110, and J819).

Pharmacotherapy and Comorbidity

Baseline pharmacotherapy was defined by dispensed prescriptions up to 6 months preceding study inclusion date with the following medications: acetylsalicylic acid, cholesterol-lowering drugs, vitamin K antagonists, digoxin, glucocorticoids, and nonsteroidal anti-inflammatory drugs. The following comorbidity was established: atrial fibrillation, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, arterial vascular disease, and thromboembolism. Hypertension was identified by either a hospital diagnosis for hypertension, or concurrent use of at least 2 of the following classes of antihypertensive agents within a 3-month period: α-adrenergic blockers, nonloop diuretics, vasodilators, β-blockers, calcium-channel blockers, and renin-angiotensin system inhibitors, as previously validated.[30] Diabetes mellitus was defined by either hospital diagnoses, or use of glucose-lowering agents.[31] Smoking history and alcohol consumption was defined by use of pharmacotherapy, therapeutic interventions, or diagnoses related to smoking or alcohol abuse, respectively (see Table S1 for codes).[27,32] The respective *ICD*, Anatomical Therapeutical Chemical, and Sundhedvæsenets

Table 1. Overview of *ICD*, ATC, and SKS Codes

Comorbidity	ICD-10/ICD-8
Arterial vascular disease	I21 to I22, I70, 410, and 440
Atrial fibrillation	I48 and 4279
Diabetes mellitus	E10 to E14 and 250
Thromboembolism	I26, I63, I64, I74, G458, G459, 433 to 438, 444, and 450
Hypertension	I10 to I15 and 400 to 404
Renal disease	N03, N04, N17 to N19, R34, I12, I13, and 582 to 588
Chronic obstructive pulmonary disease	J42, J44, and 490 to 492

Pharmacological Treatments	ATC/SKS
Acetylsalicylic acid	B01AC06
Nonsteroidal anti-inflammatory drugs	M01A
Vitamin K antagonists	B01AA
Digoxin	C01AA
Cholesterol-lowering drugs	C10A
Systemic glucocorticoids	H02AB
TNF inhibitors	L04AB01, L04AB02, L04AB04, and BOHJ18A1-3
Hypertension (α-adrenergic blockers, nonloop diuretics, vasodilators, β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors)	C02A, C02B, C02C, C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, C02DB, C02DD, C02DG, C07, C07F, C08, C09BB, and C09

ATC indicates anatomical therapeutical chemical; *ICD, International Classification of Diseases*; SKS, hospital procedure codes; TNF, tumor necrosis factor.

Klassifikations System codes for all examined comorbidities and concomitant medications are presented in Table 1.

Statistical Analysis

SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC) and STATA software (version 14; StataCorp LP, College Station, TX) were used to perform the statistical analyses.

Baseline characteristics for cohort participants were presented as frequencies and percentages for categorical variables and as means with SDs for continuous variables. Differences between parameter estimates within the models were analyzed using unpaired *t* tests and χ^2 tests, as appropriate. Age, follow-up time, and calendar year (divided into bands of 1-year periods) were included as time scales. Incidence rates of new events per 1000 person-years were reported. Multivariable Poisson regression models adjusted for age, sex, calendar year, comorbidity, concomitant medications, socioeconomic status, alcohol consumption, and smoking history were fitted to estimate incidence rate ratios (IRRs). For all analyses, a 2-tailed *P* value <0.05 was considered statistically significant, and 95% confidence intervals (CIs) were provided. Model assumptions, including absence of interaction between covariates, were tested and found to be valid for all covariates.

Sensitivity Analyses

The diagnosis of HF in the Danish National Registers has been shown to be under-reported with a sensitivity of 30% to 50% but a specificity of 99%.[33] To increase the sensitivity of the HF end point, we carried out an analysis where we changed the definition of HF to either a prescription of loop diuretics or a HF diagnosis. Also, to assess the impact of an HF secondary diagnosis, we performed a sensitivity analysis where only a primary diagnosis of HF was considered as an outcome.

Tumor necrosis factor (TNF) alpha inhibitors are frequently used to treat RA, often alongside disease-modifying antirheumatic drugs.[34] A few studies have suggested that treatment with TNF inhibitors may promote HF.[35,36] However, more-recent studies have reported a preventive effect of TNF inhibitors on overall cardiovascular risk and no significant impact on the risk of HF.[37,38] In the present study, we conducted a further sensitivity analysis where we included treatment with TNF inhibitors (infliximab, etanercept, and adalimumab [see Table 1 for Anatomical Therapeutical Chemical/Sundhedvæsenets Klassifikations System codes]) in multivariable regression models to estimate the impact of these agents on our primary findings.

RA is a chronic disease, and, consequently, there is a marked delay from onset of symptoms to first (in-patient or out-patient) consultation and diagnosis.[39] Moreover, studies have shown that patients with RA with longer disease duration have a higher risk of cardiovascular adverse events compared with those with shorter disease duration.[40] Thus, an inception study design, where subjects with prevalent RA are excluded at baseline, may underestimate the true RA-related effect. For the present study, we therefore selected a prevalent study design to better represent patients with RA in the general population. However, in order to assess the risk of HF in patients with new-onset RA, we also conducted a sensitivity analysis comprising all Danish citizens aged ≥18 years included on January 1, 2002, without a history of RA and HF. These subjects were followed until the occurrence of HF, migration, death, or December 31, 2012. To ensure an accurate allocation of exposure time, we used a time-dependent approach that allowed subjects who developed RA during the study time to contribute with time at risk in the reference group until the RA index date.

In line with many autoimmune disease, RA affects women more often than men with an average sex ratio of 3:1.[41] We therefore also performed a sex-stratified analysis. Last, to ensure accurate recording of covariates that could change over time, we conducted an analysis where the information on comorbidities and concomitant medication was updated during follow-up.

Ethics

The Danish Data Protection Agency approved the present study (ref. 2007-58-0015, int. ref: GEH-2014-018). The information on study population was encrypted and rendered anonymous by Statistics Denmark. Retrospective observational studies do not require ethical approval in Denmark.

Results

Baseline Characteristics

From January 1, 2008 to December 31, 2012, a total of 4 361 869 subjects were found eligible and included in the study. Individuals with incomplete information on migration and subjects with previous known HF (n=56 644) were excluded at the study start. A total of 24 343 subjects were identified with RA from 1978 until the study index date. Mean (SD) disease duration (defined as time between first RA diagnosis and study start) at baseline was 8.1 (5.9) years. These patients were compared with the reference population of 4 280 882 individuals without RA. During the study period, a total of 49 879 and 744 patients with incident HF were identified among the reference population and the patients with RA, respectively. At study baseline, patients with RA were older than the reference population and had a higher prevalence of hypertension and diabetes mellitus. Furthermore, there were more females in the RA group, and compared with the reference population, RA patients had an increased use of nonsteroidal anti-inflammatory drugs, glucocorticoids, and acetylsalicylic acid.

A flow chart of the study population is illustrated in Figure, and baseline characteristics for the study population are presented in Table 2.

Risk of HF in Patients With RA

The results showed a significant association between RA and incident HF (Table 3). Overall incidence rates of HF were 2.43 (95% CI, 2.41–2.45) and 6.64 (CI 6.18–7.13) per 1000 person-years for the reference population (49 879 cases) and RA (744 cases), respectively (Table 4).

The time-dependent multivariable Poisson regression analyses, adjusted for age, sex, and calendar year, showed

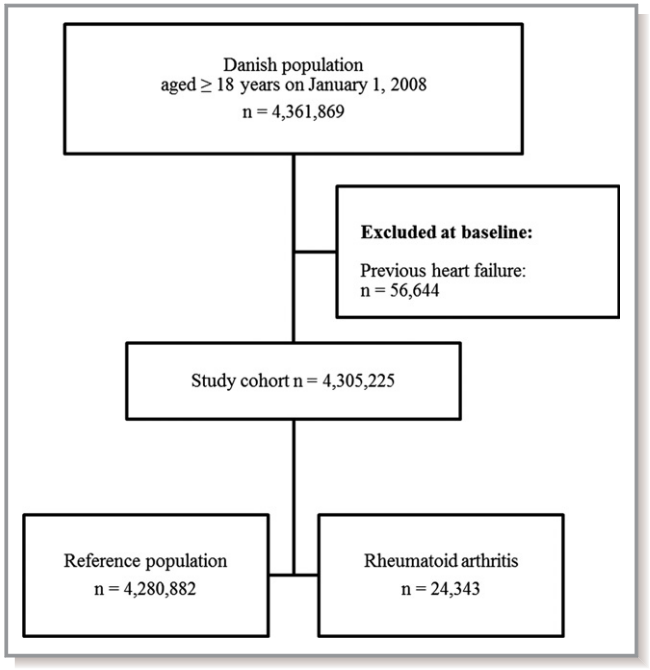

Figure. Flow chart of selection of study population.

increased risk of HF in patients with RA compared with the reference population with IRR 1.64 (CI, 1.53–1.77). The risk remained significant with IRR 1.30 (CI, 1.17–1.45) in the fully adjusted analysis when controlling for age, sex, calendar year, comorbidity, concomitant medications, socioeconomic status, alcohol consumption, and smoking history (Table 3).

Sensitivity Analyses

When the primary study end point was modified to include a prescription for loop diuretics and a hospital diagnosis of HF, the RA-associated increased risk of HF remained statistically significant with IRR 1.30 (CI, 1.26–1.35) in the fully adjusted analysis. When we excluded all subjects, who were registered with HF as a secondary diagnosis and only focused on subjects with HF as a primary diagnosis (27 303 cases), the association between RA and HF was not considerably altered (IRR, 1.43 [CI, 1.25–1.65]).

Including treatment with TNF inhibitors in the Poisson regression models had no significant impact on the risk estimates of HF in RA patients (Table 3). When we adjusted for concomitant medication and comorbidity that was continuously updated throughout the study period, the results for RA (IRR, 1.22 [CI, 1.13–1.31]) were also comparable with the primary analysis. Concerning the impact of sex on risk of HF in patients with RA, we found a nominally slightly increased IRR (1.34 [CI, 1.18–1.53]) for females compared with males (IRR, 1.22 [CI, 1.02–1.47]), but there was no statistical significant difference between the 2 groups.

Table 2. Baseline Characteristics of the Study Population

	Reference Population (n=4 280 882)	Rheumatoid Arthritis (n=24 343)
Mean (SD) age, y	48.3 (17.8)	60.7 (15.3)
Men, %	2 108 067 (49.2)	6400 (26.3)
Female, %	2 172 815 (50.8)	17 943 (73.7)
Mean (SD) socioeconomic status	2.0 (1.4)	1.9 (1.3)
Alcohol consumption, %	59 614 (1.4)	235 (1.0)
Smoking ever, %	410 101 (9.6)	4353 (17.9)
Comorbidity, %		
Arterial vascular disease	30 502 (0.7)	438 (1.9)
Atrial fibrillation	33 668 (0.8)	478 (2.0)
Diabetes mellitus	145 336 (3.4)	1473 (6.1)
Thromboembolism	50 493 (1.2)	659 (2.8)
Hypertension	486 052 (11.4)	5353 (22.0)
Renal disease	8163 (0.2)	116 (0.5)
COPD	25 360 (0.6)	464 (2.0)
Medications, %		
Acetylsalicylic acid	316 861 (7.4)	3545 (14.5)
NSAID	528 721 (12.4)	8457 (34.7)
Vitamin K antagonists	52 843 (1.2)	665 (2.7)
Digoxin	28 270 (0.7)	407 (1.7)
Cholesterol-lowering drugs	373 137 (8.7)	3483 (14.3)
Systemic glucocorticoids	79 033 (1.9)	5084 (20.9)

COPD indicates chronic obstructive pulmonary disease.

When we conducted an inception cohort study comprising the entire Danish population aged ≥18 years followed from January 1, 2002, a total of 5 291 138 subjects with no history of RA and HF were eligible for analysis at the study start. Of these subjects, 14 691 developed new-onset RA and 138 567 were hospitalized for HF during a maximum follow-up of 11 years. Overall incidence rates of incident HF were 2.58 (CI, 2.56–2.59) and 6.32 (CI, 5.73–6.98) per 1000 person-years for the reference population (38 175 cases) and patients with RA (392 cases), respectively. Correspondingly, the fully adjusted IRRs for incident HF were 1.44 (CI, 1.26–1.65) in patients with RA in this analysis.

Discussion

In the present cohort study of the entire Danish population, we found an increased risk of incident HF in patients with RA independent of measured risk factor. Results were supported by several sensitivity analyses. These findings suggest the need for increased awareness regarding the risk of incident HF in patients with RA.

Table 3. Risk of HF Associated With Rheumatoid Arthritis Presented as IRRs With 95% CIs

	IRR for HF	95% CI	*P* Value
Adjusted for age, sex, and calendar year	1.64	1.53 to 1.77	<0.001
Adjusted for age, sex, calendar year, comorbidity*, medication, socioeconomic status, alcohol, and smoking	1.30	1.17 to 1.45	<0.001
Sensitivity analyses			
Fully adjusted including TNF inhibitors	1.29	1.15 to 1.43	<0.001
Fully adjusted with updated comorbidity and medications	1.22	1.13 to 1.31	<0.001
Fully adjusted with altered definition of HF†	1.30	1.26 to 1.35	<0.001
Fully adjusted (IRR of HF in females)	1.34	1.18 to 1.53	<0.001
Fully adjusted (IRR of HF in males)	1.22	1.02 to 1.47	<0.003

CI indicates confidence interval; HF, heart failure; IRR, incidence rate ratio; TNF, tumor necrosis factor.
*Comorbidity included in the analyses: arterial vascular disease, atrial fibrillation, diabetes mellitus, thromboembolism, hypertension, and renal disease.
†Altered HF definition: patients with HF identified by either a prescription of loop diuretic or hospital diagnosis.

The increased risk of cardiovascular disease and cardiovascular-related mortality in subjects with RA is well established.[2,6] Studies have reported that patients with RA exhibit a doubled risk of myocardial infarction and 60% increased risk of cardiovascular mortality compared with the general population.[42] An increased prevalence of traditional risk factors, such as diabetes mellitus, hypertension, obesity, smoking, and physical inactivity, may explain, in part, this excess cardiovascular risk in RA.[8,11] However, innate as well as adaptive immune mechanisms shared by RA and cardiovascular disease, namely atherosclerosis, have emerged as potential contributors to the heightened cardiovascular risk observed in these patients.[43,44]

HF is a growing public healthcare problem worldwide that poses a substantial economic burden on national healthcare

Table 4. Incidence Rates With 95% CIs Per 1000 Person-Years of HF and Number of Events

	Reference Population	Rheumatoid Arthritis
Overall IR (CIs)	2.43 (2.41–2.45)	6.64 (6.18–7.13)
No. of events, n	49 879	744

CI indicates confidence interval; HF, heart failure.

systems.[10,45] In recent years, research has indicated that persistent systemic inflammation may play a pivotal role in promoting the development and progression of HF through a vast array of mechanisms, including endothelial dysfunction, increased arterial stiffness, and adverse myocardial and vascular remodeling.[12,16,18] Notably, proinflammatory mediators implicated in HF seem to overlap those involved in various chronic inflammatory diseases, such as psoriasis, inflammatory bowel disease, and RA.[12,46,47] Moreover, RA has also been associated with increased arterial stiffness and endothelial dysfunction that may contribute to development of HF by increased myocardial afterload and reduced coronary flow reserve.[15,19] Also, RA has been associated with left ventricular concentric remodeling and systolic and diastolic left ventricular dysfunction, respectively.[13,14,17,21] Even at an early course of the disease, patients with RA are more likely to display significantly elevated levels of circulating cardiac biomarkers (eg, troponins, pro-B-type natriuretic peptides) that are recognized as strong predictors of cardiac diseases, including HF.[48] On these grounds, it is highly conceivable that a chronic systemic inflammatory state in RA may confer an increased risk of HF that is independent of traditional cardiovascular risk factors.

Allthough previous studies based on selected populations have suggested that patients with RA are at increased risk of developing left ventricular dysfunction and HF, only a single nationwide study has been conducted and very recently reported.[14,17,20,21,49] Indeed, a register-based Swedish study found a 22% to 27% increased risk of HF in patients with RA, with the increased risk being similar for those with ischemic versus nonischemic HF and strongest for subjects positive for rheumatoid factor, respectively.[20] Notably, RA is a chronic disease and there is often a significant delay from onset of symptoms to first healthcare visit and diagnosis.[39,40] To give a better representation of patients with RA in the general population, we therefore chose a prevalent study design for our main analysis, where we did not exclude patients with a history of RA before the study start. However, we also performed a sensitivity analysis where we reported IRRs for new-onset RA with a maximum follow-up of 11 years and found comparable results. These findings add importantly to the evidence provided in the previous studies by demonstrating a higher risk of incident HF in RA, which appears to be independent of traditional cardiovascular risk factors.

Besides shared immunoinflammatory mechanisms and over-representation of cardiovascular risk factors, the increased use of glucocorticoids and TNF inhibitors in patients with RA may have contributed to our findings. Glucocorticoids have multiple adverse effects, including hypertension and salt-water retention, and limited evidence has suggested that a long-term use of large doses may accelerate HF.[50] On the other hand, data regarding risk of HF in patients with RA treated with TNF inhibitors are inconclusive.[35–38] In the present study, however, we adjusted for glucocorticoids and TNF inhibitors in multivariable regression analyses and found increased risk of HF in RA patients independent of these agents.

Taken together, the present analysis suggests that patients with RA have an increased risk of HF that cannot be explained by established risk factors.

Strengths and Limitations

Notable strengths of the present study include a large number of unselected participants, adjustment for important confounders, the high accuracy of the prospectively recorded nationwide registries, and information on tax-reported household income. Also, the Danish government-financed healthcare system guarantees care that is free of charge and readily accessible for all citizens, which minimizes the bias related to age, sex, comorbidity, and socioeconomic status. In addition, use of validated measures of exposures and outcomes, as well as a real-world setting with complete follow-up, add to the reliability of our results.

Despite these strengths, there are various potentially important limitations to be acknowledged when interpreting our findings. For example, because of the observational nature of our study, it is not possible to determine causality between RA and HF. Moreover, the registers lacked information on important confounding factors, such as echocardiographic data, circulating lipid and glucose levels, clinical signs of HF, blood pressure, and body mass index, although we made some efforts to gauge these effects by use of indirect measures. Nonetheless, we cannot refute that residual confounding may have biased our estimates, and the results should be interpreted accordingly.

Furthermore, because of frequent healthcare contacts, patients with RA are more likely to be diagnosed with HF at an early stage, leading to surveillance bias. However, our sensitivity analysis with use of either a prescription of loop diuretics and/or a HF diagnosis gave comparable results with the primary analysis. Also, when analysis was restricted to cases in which HF was the primary cause of hospitalization, the results were not affected. Finally, the Danish population is predominantly of Northern European decent, and generalizability of our findings to other ethnicities should be performed with caution.

Conclusion

The results of the present nationwide study indicate an increased risk of incident HF in patients with RA. These findings add to the existing evidence of RA as a clinically relevant risk factor for HF and studies of the value of more-vigilant screening of these patients for HF are warranted.

Author Contributions

Conceived and designed the experiments: Khalid, Egeberg, Gislason, Lip, Hansen. Analyzed the data: Khalid, Egeberg, Lip. Wrote the manuscript: Khalid, Lip, Hansen. Revision of manuscript for critical contents: Khalid, Egeberg, Ahlehoff, Gislason, Lane, Lip, Hansen. Supervision: Hansen, Lip, Lane, Gislason. Joint senior authors: Hansen, Lip. All authors approved the final manuscript. Khalid had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Procedure and diagnoses codes for smoking history.

Diagnosis	**Code (ICD)**	**Excluding**
COPD	490-492 (ICD-8), J42, J44	
Lung cancer	162 (ICD-8), C33, C34	
Nicotine dependence	F17	
Tobacco abuse counseling	Z716	
Tobacco use	Z720	Z720D (Never smoker)
Toxic effect of tobacco and nicotine	T652	
Tobacco smoking	Z587	Z587A (Passive smoking)
Tobacco use, amount	VRB0	
Treatment/procedure	**Code (SKS)**	**Excluding**
Treatment with drugs used in nicotine dependence	BRHT	
Consultation for smoking cessation (pregnant)	BKUA32	
Intervention regarding smoking cessation	BQFT01	
Treatment with regards to smoking cessation	BRXT	
Education regarding smoking cessation	BVDT	
Dialog regarding smoking cessation	BQFS01	
Smoker, tried to motivate cessation	ZZP0020	
Smoker, not tried to motivate cessation	ZZP0021	
Smoker	ZZP01A1A	
Smoker, stopping [cessation within last 6 months]	ZZP01A1B1	
Former smoker	ZZP01A1B2	
COPD rehabilitation	ZZ5730	

Prescriptions	**Code (ATC)**	**Excluding**
Varenicline	N07BA	
Bupropion	N06AX12	